
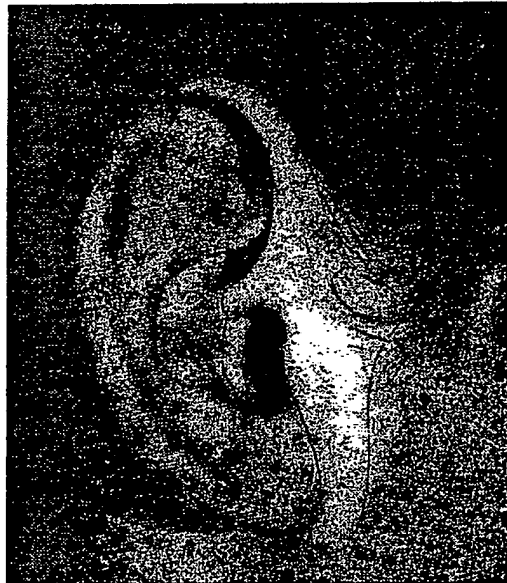




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB92/00878 (22) International Filing Date: 15 May 1992 (15.05.92) (30) Priority data: 9110652.6 15 May 1991 (15.05.91) GB (71) Applicant (for all designated States except US): STIEFEL LABORATORIES, INC. [US/US]; 2801 Ponce de Leon Boulevard, Suite 850, Coral Gables, FL 33134-6988 (US). (72) Inventors; and (75) Inventors/Applicants (for US only) : WOOD, John, Martin [GB/DE]; SCHALLREUTER, Karin, Uta [DE/DE]; Feldbehnekehre 16, D-2085 Quickborn (DE). (74) Agent: BURFORD, Anthony, Frederick; W.H. Beck, Greener & Co., 7 Stone Buildings, Lincoln's Inn, London WC2A 3SZ (GB).		(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), NO, PL, RO, RU, SE (European patent), US. Published <i>With international search report.</i>
(54) Title: COMPOSITION AND METHOD OF TREATING DEPIGMENTATION DISORDERS		
<div style="display: flex; justify-content: space-around; align-items: flex-end;"> <div style="text-align: center;">  <p>BEFORE TREATMENT</p> </div> <div style="text-align: center;">  <p>AFTER TREATMENT</p> </div> </div>		
(57) Abstract <p>Vitiligo and other tyrosinase-positive depigmentation disorders are treated by topical application of a pseudocatalase and subsequent exposure to a sub-minimal erythema dose of UVB light. After a course of treatment, pigmentation of the affected areas can be maintained by treatment with the pseudocatalase without UVB light treatment. The preferred pseudocatalases are transition metal co-ordination complexes, especially manganese (II) bicarbonate.</p>		

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COMPOSITION AND METHOD OF
TREATING DEPIGMENTATION DISORDERS

5 The present invention relates to the treatment of
tyrosinase-positive depigmentation disorders and has
particular application to the treatment of vitiligo. It
provides compositions for said treatment and methods of
said treatment.

10 Vitiligo is a chronic depigmentation disorder in which
the patient has unsightly white patches or spots which are
caused by localized loss of pigment and are very liable to
sunburn. Although the condition is not debilitating, it is
15 often emotionally stressful to the patient. The cause
presently is unknown but it has been speculated that it
results from an autoimmune response, involvement of the
nervous system or a toxic effect on melanocytes. Usually,
the only treatment is the use of skin-colouring cosmetics
20 to disguise the patches or, in the case of Blacks and
Indians, of depigmenting agents such as hydroquinone to
depigment the remaining pigmented skin. Some limited
success in treatment has been reported using the so-called
PUVA method.

25 In the PUVA method, methoxsalen (ie. 8-methoxy
psoralen) or, less usually, other psoralens is administered
orally and the patient subsequently exposed to UVA light.
Psoralens are plant extracts and have been known since
30 ancient Egyptian times to act as photosensitizers. The
psoralen is given systemically and hence the
photosensitizing effect is not localized and, since this
effect is in the UVA range (320-400 nm), the patient must
wear special glasses during everyday life in order to
35 prevent eye damage. Further, side effects of PUVA include
nausea, erythema, oedema, dizziness, headache,

vesiculation, bulla formation, onycholysis, acneiform eruption and severe skin pain. Long term risks include skin cancer, epidermal dystrophy, premature skin aging, cataract formation, and alterations in the immune system.

5 The treatment is believed to be toxic to normal lymphocytes and Langerhans' cells. Accordingly, the treatment usually is limited to elderly patients or to two years duration. It has recently been proposed to mitigate some of the risks of PUVA by bathing the patient in a psoralen bath.

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Other tyrosinase-positive depigmentation disorders include Hermansky-Pudlak Syndrome.

15 It has now surprisingly been found that vitiligo and other tyrosinase-positive depigmentation disorders can be effectively treated by exposing a patient to UVB light (290-320 nm) after topical application of manganese (II) bicarbonate or other pseudocatalase. Further, it has been found that, following pigmentation by said treatment, a
20 level of pigmentation in affected areas can be retained, at least for a period of time, by topical application of the pseudocatalase without UVB exposure.

We have disclosed in a co-pending Patent Application
25 of the same priority and filing dates and corresponding to UK Patent Application No. 9110651 that pseudocatalase can be used topically to enhance sun tanning.

By pseudocatalase, we mean a plasma membrane permeable
30 physiologically acceptable compound which catalyzes the dismutation of H_2O_2 in vivo in analogous manner to catalase.

Without wishing to be bound to any particular
hypothesis, it is believed that vitiligo and other
35 tyrosinase-positive depigmentation disorders are caused by a deficiency of catalase which permits a higher than normal

peroxide ion concentration in melanocytes. Since tyrosinase is inactivated by peroxide ion, the tyrosinase-catalyzed oxidation of l-tyrosine to l-dopa required for melanin biosynthesis is inhibited. Further, since peroxide ion is photochemically reduced to hydroxyl ion, there is a concomitant increase in hydroxyl ion production.

Exposure of the skin to UVB radiation generates superoxide anion radicals which is a preferred substrate for human tyrosinase (40 times better than oxygen) thereby promoting melanin formation. However, the superoxide anion radicals are dismutated into dioxygen and peroxide ion causing an undesirable increase in hydroxyl ion concentration unless catalase or some other competing mechanism removes peroxide ion. Thus, the presence of a pseudocatalase is believed to allow sufficient UVB exposure for superoxide anion radical formation to promote pigmentation in catalase deficient areas without burning or other cell damage.

According to a first aspect of the present invention, there is provided the use of a pseudocatalase in the manufacture of a topical medicament for the treatment of a tyrosinase-positive depigmentation disorder.

In a second aspect, the invention provides a topical composition comprising a pseudocatalase and a physiologically acceptable topical vehicle therefor.

In a third aspect, the invention provides a pseudocatalase for use in the treatment of a tyrosinase-positive depigmentation disorder.

In a fourth aspect, the invention provides a method of treating a tyrosinase-positive depigmentation disorder which comprises applying to at least the depigmented areas

of the skin of a patient suffering therefrom an effective amount of a pseudocatalase and thereafter exposing the treated skin to UVB light to induce melanin formation in the depigmented areas.

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As mentioned previously, the invention has particular application to the treatment of vitiligo but can be applied to the treatment of other tyrosinase-positive depigmentation disorders, for example Hermansky-Pudlak Syndrome.

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The pseudocatalase can be any physiologically acceptable compound which catalyzes the dismutation of hydrogen peroxide. Some compounds such as Mn(II) bicarbonate are already known to be pseudocatalases and others can be determined by simple screening tests.

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The presently preferred pseudocatalases are transition metal co-ordination complexes in which the inductive effect of the electron acceptor ligand enhances the redox effect of the metal on hydrogen peroxide dismutation. Usually, the metal will be Cu(I), Fe(II) or, especially Mn(II) and the ligand will be bicarbonate. It is especially preferred that the pseudocatalase is Mn(II) bicarbonate complex. Said complex readily can be prepared by contacting manganous chloride with excess bicarbonate in aqueous solution.

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The pseudocatalase is formulated in a topical vehicle for use. Conveniently, the vehicle comprises a hydrophilic cream to which an aqueous solution or suspension of the pseudocatalase is added to form a cream or lotion. Alternatively, the vehicle can be a bath oil although any other compatible topical vehicle can be used to provide a topical composition.

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Preferably, the composition contains calcium ions, suitably added as calcium chloride, to compensate for a calcium defect which appears to be present in vitiliginous skin. Usually, the calcium ion concentration will be 5 to 20 mmol

The composition can contain components such as emollients, perfumes etc conventionally used in topical preparations.

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Usually, the topical composition is applied twice a day to at least the depigmented areas of skin, usually to the entire skin surface. After at least one of said applications, the patient is exposed to UVB light after a short delay, usually about 20 to 60 minutes, to allow for transport of the pseudocatalase into the epidermis. The UVB exposure is limited to prevent erythema and is increased over the period of treatment from a few seconds to about 5 minutes as the minimal erythema dose increases with UVB tolerance. The course of treatment is continued for several months until there is an acceptable level of pigmentation in the previously depigmented areas. Thereafter, pigmentation is maintained by continuing daily application of the topical composition, possibly with reduced frequency, without UVB exposure. If and when pigment is lost from the affected areas, the exposure to UVB light is recommenced for as long as necessary to restore pigmentation.

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The invention is illustrated in the following non-limiting Examples.

Example I

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Manganous chloride (380 mg) was added to a solution of sodium bicarbonate (2.3 g) in purified water (3.0 ml) at

ambient temperature. The mixture was allowed to stand until the evolution of gas had ceased. The resultant pinkish brown liquid was mixed with a hydrophilic cream (100 g, Neribase) to provide a white cream.

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Neribase is a cream vehicle containing Macrogol stearate 2000; stearic alcohol; liquid paraffin; white soft paraffin; polyacrylic acid; sodium hydroxide; disodium EDTA (i.e. ethylenediaminetetraacetic acid disodium salt); methyl and propyl Paraben (i.e. 4-hydroxybenzoic acid methyl and propyl esters); and water.

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Example II

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The white cream of Example I was applied twice daily (morning and either afternoon or evening) to the depigmented areas (vitiligo spots) of several patients suffering from vitiligo. After about 20 minutes following one of said applications, the affected areas were exposed to UVB light for a short period of time to provide a sub-minimal erythema dose. As the patient's tolerance to UVB light increased, the exposure time was increased from a few seconds to a maximum of about 5 minutes. In all cases, the vitiligo spots were significantly pigmented after a course of treatment of between 3 and 6 months.

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The accompanying Figures I and II show a typical improvement in the vitiligo patients treated. Both figures show the ear of the same patient. When the patient presented at the clinic, she had several large vitiligo spots including one in the region of the right ear (Fig. I). After three months pseudocatalase/ UVB treatment as described above, many of the vitiligo spots had decreased substantially in size including the right ear spot (Fig. II). Pseudocatalase/UVB treatment of this patient continued for a further three months, by which time there

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was a further substantial reduction in size of the vitiligo spots. The patient was then maintained with pseudocatalase treatment alone.

5 Example III

10 The procedure of Example 1 was repeated using creams to which calcium chloride had been added to provide 5 mmole calcium ion content. 18 patients were treated for a mean duration of 4.2 months; 14 of these patients had a partial response and 2 showed a marked, although not complete, pigmentation of vitiliginous skin areas.

15 Example IV

20 The procedure of Example 1 was repeated using creams to which calcium chloride had been added to provide 10 mmole calcium ion content. 12 patients were treated for a mean duration of 2.25 months; all had a partial response but none showed significant pigmentation of vitiliginous skin areas.

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CLAIMS

- 5 1. A topical composition comprising a pseudocatalase and
a physiologically acceptable topical vehicle therefor.
2. A composition as claimed in Claim 1, which contains 5
to 20 mmol calcium ions.
- 10 3. A topical composition as claimed in Claim 1, wherein
the pseudocatalase is a transition metal co-ordination
complex.
- 15 4. A composition as claimed in Claim 3, wherein the
pseudocatalase is a Cu(I), Fe(II) or Mn(II) co-ordination
complex.
- 20 5. A composition as claimed in Claim 3, wherein the
ligand of said co-ordination complex is bicarbonate.
6. A composition as claimed in Claim 5, wherein the
pseudocatalase is a Mn(II)-bicarbonate complex.
- 25 7. A composition as claimed in Claim 6, wherein the
Mn(II)-bicarbonate complex has been obtained by contacting
manganous chloride with excess sodium bicarbonate in
aqueous solution.
- 30 8. A method of pigmenting skin depigmented by a
tyrosinase-positive depigmentation disorder which comprises
applying to at least the depigmented areas of the skin an
effective amount of a pseudocatalase and thereafter
exposing the treated skin to UVB light to induce melanin
35 formation in the depigmented areas.

9. A pseudocatalase for use in the treatment of a tyrosinase-positive depigmentation disorder.

10. The use of a pseudocatalase in the manufacture of a
5 topical medicament for the treatment of a tyrosinase-positive depigmentation disorder.

11. Use of a pseudocatalase to pigment skin depigmented by
10 a tyrosinase-positive depigmentation disorder.

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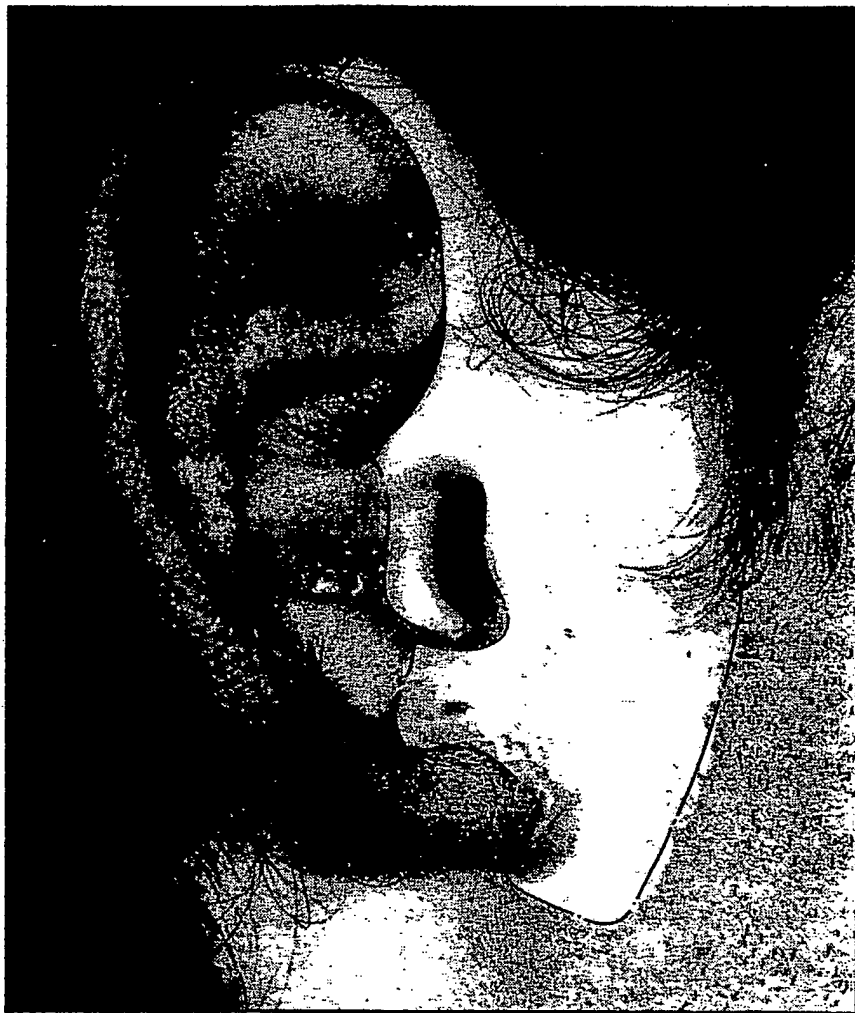
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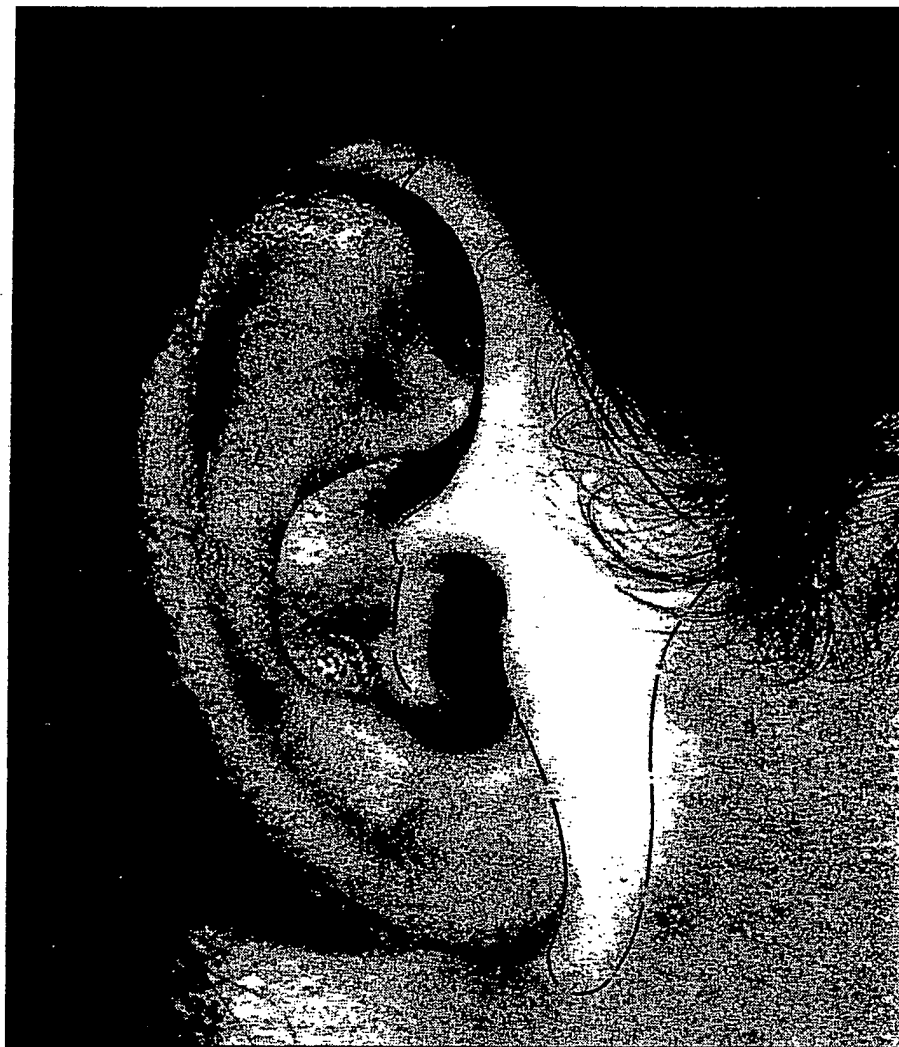
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BEFORE TREATMENT

FIG. I

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AFTER TREATMENT

FIG. II

INTERNATIONAL SEARCH REPORT

International Applic. No. PCT/GB 92/00878

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5 A 61 K 33/24 A 61 K 33/32 A 61 K 33/34 A 61 K 33/26		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0424033 (POLA CHEMICAL INDUSTRIES INC.) 24 April 1991, see the whole document ---	1,3-4
A	FR,A,2287899 (L'OREAL) 14 May 1976, see page 3, lines 3-11; page 9, lines 20-21; page 10, lines 1-13; claims ---	1,3-4,9 -11
X	Patent Abstracts of Japan, vol. 14, no. 314 (C-737)[4257], 5 July 1990, & JP,A,2108612 (ZHIZEN K.K.) 20 April 1990, see the abstract ---	1,3-4
A	Patent Abstracts of Japan, vol. 13, no. 308 (C-617)[3656], 14 July 1989, & JP,A,196107 (KANEBO LTD) 14 April 1989, see the abstract ---	1,3-4
X	AU,B, 73343 (WALLICZEK) 25 February 1982, see the whole document --- -/-	1,3-4
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
10-07-1992		07. 08. 92
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,A	STN File Supplier, Karlsruhe DE, File Chemical Abstracts, & CA, vol. 114, no. 21, 27 May 1991, (Columbus, Ohio, US), Y. KONO: "Manganese calatase", see abstract no. 202133d, & KASSEI SANSO, FURI RAJIKARU, 1990, 2(1), 18-26, see the abstract	1
A	<p>---</p> <p>AU,B, 44552 (HAUSLER) 28 August 1980, see the whole document</p> <p>-----</p>	1

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9200878

SA 59486

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/07/92.
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EP-A- 0424033	24-04-91	JP-A- 3204805	06-09-91
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